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|---|---|
| YU, MISOOK | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/499,662 | Applicant(s) SERIZAWA ET AL. | |
|---|---|---|---|
| | Examiner Misook Yu | Art Unit 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-20,22-29,41-55,61-81,88-90,103-105 and 107* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *14,15,62-78,88-90 and 107* is/are allowed.

6)☒ Claim(s) *1-13,16-20,22-29,41-55,61,79-81 and 103-105* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2,17* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election with traverse of group 1 with species SEQ ID NO: 107 and 117 and a species rheumatoid arthritis in Paper No. 18 is acknowledged. The traversal is on the ground(s) that the requirement for election of the species is not proper under rule of MPEP 803.02 . This is not found persuasive because all of the species are protein with either 218 amino acids (total 8 such IgG light chains) or 415 amino acids (total 6 such IgG heavy chains) and it is well known in the art that function of proteins is unpredictable even with close structural relationship to a known protein and therefore searching all of the species would put serious burden on examiner.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-20, 22-29, 41-55, 61-81, 88-90103-105, 107 and pending and examined as they are drawn to the elected species, SEQ ID NO: 107 and 117, and rheumatoid arthritis initially. When the elected product species is free of the art, then search will be expanded to the generic claims. As for the species of the intended use of the product, the elected rheumatoid arthritis will be examined.

### *Priority*

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). Receipt is acknowledged of papers (JP 10-276681 and JP 10-276682) submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Acknowledgment is made of applicant's claim for foreign priority based on JP applications (9-82953 and 9-169088, and 9-276064). It is noted, however, that applicant has not filed a certified copy of the JP applications as required by 35 U.S.C. 119(b) and this examiner was not able to locate the certified copies of the applications either in parent Application No. 09/053,583, filed on 04/01/1998, or parent Application No. 09/408,646, filed on 09/30/1999.

***Information Disclosure Statement***

The information disclosure statements filed on 4-10-2002, Paper No. 13 and on 8-13-2002 Paper No. 17 list identical references. The two IDS are duplicate, therefore only one (Paper No. 17) of them is considered.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 10, 16-19, 22-24, and 25-29 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "A molecule having an antigen binding region specific for an epitope of the Fas antigen, said epitope being conserved between a primate and a non-primate animal" but it is not clear what the metes and bounds are for the phrase. Neither the claims nor the specification defines the phrase and one in ordinary skill in the art would not clearly understand what is being claimed for patent protection by the term in light of Figure 5 of Watanabe-Fukunaga et al (February 15, 1992, The Journal of Immunology, Vol. 148, page 1274-1279) that shows the human and mouse Fas antigens are conserved throughout the entire amino acid sequence of the human and mouse Fas proteins. The specification at page 99 line 7-8 says that SEQ ID NO:1 (epitope p105 in Fig. 4 of the instant specification) is "a region which is conserved between human Fas and mouse Fas" but this sentence does not define what is being claimed in claim 1.

Claim 6 recites "conserved, mammalian Fas epitope but it is not clear what the metes and bounds are for the phrase.

Claim 22 recites an antigen binding region specific for an epitope of the Fas antigen, said epitope being conserved between a primate and a non-primate animal" but it is not clear what the metes and bounds are for the phrase.

All the claims depends on claims 1, 6, and 22 are also rejected for being indefinite.

For compact prosecution purpose of the instant application and for the prior art search part of this office action, the examiner will assume that definition of "conserved" amino acid sequence of Fas between human and mouse is the extracelluar domain, since the specific HFE7A monoclonal antibody disclosed in the instant application is generated from the extracellular domain of human Fas antigen and Watanabe-Fukunaga et al., February 15, 1992, The Journal of Immunology, Vol. 148, page 1274-1279 at Figure 5 at page 1278 and at page 1277 left column teach the extracellular domain of human (amino acids #1-149) and of the mouse Fas antigens are conserved. However, this treatment does not relieve applicant the burden of responding to this rejection.

Claim 61 recites "in cells having an abnormality in the Fas/Fas ligand system" but it is not clear what the metes and bounds are for the phrase.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 9, 17, 19, 25, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had **possession** of the claimed invention. The claims are drawn to a genus of molecules that binds to a conserved Fas epitope (claims 1-6), which is antibody (claims 10 and 11), IgG antibody (claim 16), humanized (claims 17 and 18), and which induces apoptosis in normal and abnormal cells (claim 19). Since the specification at page 99 lines 7-8 says that SEQ ID NO:1 (epitope p105 in Fig. 4) is "a region which is conserved between human Fas and mouse Fas", the claims are interpreted as molecules that bind to the epitope p105 in Fig. 4.

The specification discloses:

1) subcloning of human Fas-MAIC, cloning of cDNA heavy chain and light chain using hybridoma HFE7A at Fig. 1.
2) antibody produced by hydridoma HFE7A recognizes epitopes listed at page 94 and 95 at Fig. 2.
3) several IgG subclones binds to human Fas fusion protein detected by absorbance at 405 nm at Figs 28-30.
4) cytotoxicity of humanized HFE7A to WR19IL12a at Fig. 30.
5) binding of human Fas fusion protein at Fig. 45, competitive binding at Fig. 46, apoptosis of T cells by the supernatants Fig. 47, by supernatant of cells expressing heavy and light chain of humanized HFE7A, all of them bind the protein.
6) binding of humanized HFE7A at Fig. 64, competitive binding by same supernatant at Fig 65, apoptosis of WR19IL12a by same supernatant at 66 by supernatant by transformed COS-7 cells.
7) binding activity of supernatant expressing the humanized antibody to human Fas at Fig. 72 and 73.
8) The preparation of the HFE7A antibody at page 34 by preparing the antigen a) by fusing the extracellular domain of human Fas to the extracellular domain of interleukin-3 receptor and recombinantly producing the fusion immuongen, followed by immunizing mice with the immunogen of step a), followed by verification of binding of the antibody produced by the hybridomas to extracellular domain of recombinant human Fas, see page 36 1st para at page 39. HFE7A deposited according to Budapest Treaty at page 39-40, the literal support for claims 54 and 55 are at pages 64 and 65 but no data shown, therefore it is assertion at pages 64 and 65.
9) Reference Example 1 at page 68 describes antigen preparation, human Fas extracellular domain fused to other human protein, this is same as the antigen prepared by Alderson et al (IDS, International Immunology, Vol. 6 pages 1799-1806).

10)Reference Example 2 at page 73 describes making and screening antibody (page 77) using WR19L12a mouse T lymphoma cells expressing human Fas and L5178YA1 expressing mouse Fas, the HFE7A, type IgG1 was selected to bind both human and mouse Fas.

11)Reference Example 3 at page 79 describe purification of the antibody. Reference Example 4 at page 81 describe cDNA cloning of HFE7A.

12)Reference Example 5 at page 89 describe preparation of recombinant HFE7A antibody. Reference Example 6 at page 93 and describe epitopte determination by ELISA, which shows that P11 peptide SEQ ID NO: 36, i.e. amino acids #100-119 shown in Fig. 3 of Itoh et al., Cell 66, page 233-43, is the best epitope for HFE7A antibody as shown in Fig. 2 of the instant application. Competitive binding of the epitopes in Fig. 4 show p105, which is SEQ ID NO: 1 of the instant application, inhibits binding of HFE7A antibody and human Fas, which leads to say "This epitopic amino acid sequence is a refion which is conserved between human Fas ad mouse Fas" page 99, line 7-8. Reference Example 7 from page 99 to 100 discloses, HFE7A prepared from human source (page 100 line 6 from bottom) is able to bind simian Fas.

13)Reference Example 8 (Table 1 at page102) from page 100 to 103 discloses HFE7A antibody induces apoptosis in normal mouse T cells; it appears that Ch3/HeJ mice used in this experiment is a normal strain. Note page 3042 left column 2$^{nd}$ para of Hartwig et., Blood vol. 99, pages 3041-3049.

14)Reference Example 9 at pages 103 and 104 discloses MRL gld/gld mice with mutation in gene which serves as "systemic lupus erythematosus-like autoimmue diseases" model, who received HFE7A antibody has less swelling and the antibody also reduces Fas-expressing T cells. Reference Example 10 at page 104 and Fig. 5 disclose HFE7A does not cause liver toxicity and Reference Example11 discloses mice who received HFE7A

do not develop fulminant hepatitis but mice who received anti-mose Fas Jo2 develop fulminant hepatitis.

15)Reference Example 12 at page 106 and Fig. 7 disclose that HFE7A reduces symptoms of collagen-induced arthritis in mice and Table 2 at page 109 discloses that HFE7A causes apoptosis of in vitro synovial cells taken from rheumatoid arthritis patients.

16)The specification from page 109 to page 153 describe cloning and humanization of HFE7A and sequencing of the humanized HFE7A antibody. Reference Example 16 at page 153 discloses expression of the humanized HFE7A heavy and light chains in COS-1 cells.

17)Reference Example 17 at 155 describes quantification of the antibody using ELISA. Reference Example 18 at page 156 describes Fas and anti-Fas binding assay. Fig. 29 and Reference Example 19 at pages 158 and 159 discloses the supernatant of COS-1 cells expressing the humanized HFE7A antibody competitively binds to recombinant human Fas (or inhibits binding of HFE7A to the Fas).

18)Reference Example 20 at pages 160 and 161 and Fig. 30 discloses that WR19L12a mouse T lymphoma cells the supernatant of COS-1 cells expressing the humanized HFE7A antibody induces apoptosis of WR19L12a mouse T lymphoma cells.

19)Reference Examples 21 and 22 from pages 161 to 182 describes another rounds of humanizing the mouse anti-human Fas HFE7A by site directed mutagenesis and sequencing verification of the heavy and light chains.

20)Reference Example 23 from page 182-187 describes high-level expression vectors using the humanized light chains and heavy chains. Reference Examples 24 at page 187-188 describe expression of the humanized heavy and light chains in COS-1 cells.

21)Fig. 45 and Reference Example 25-27 describe that the second generation humanized antibodies describe in Reference Example 24 is able to bind the recombinant human Fas (Fig. 45), inhibits binding of

HFE7A to the Fas (Fig. 46), and induces apoptosis in WR19L12a mouse T lymphoma cell (Fig. 47).

22) Examples 1-3 at pages 194-232 describe making Eu type humanized HFE7A, Examples 4 at pages 233-234 describe expression of the Eu humanized heavy and light chains in COS-7cells.

23) Example 5-8 at pages 234-236 describe that the Eu humanized antibodies describe in Example 1 are able to bind the recombinant human Fas (Fig. 64), inhibits binding of HFE7A to the Fas (Fig. 65), and induces apoptosis in WR19L12a mouse T lymphoma cell (Fig. 66).

24) Examples 9 and 10 at page 236-244 describe another rounds of humanizing HFE7A antibody by grafting CDR, not FR and Example 11 at page 244 describes expression of the antibody in Examples 9 and 10 in COS-1 cells and Example 12 describes quantification of the antibody using ELISA.

25) Example 13-15 at pages 246-247 describe that the humanized antibodies describe in Example 9and 10 are able to bind the recombinant human Fas (Fig. 72), inhibits binding of HFE7A to the Fas (Fig. 73), and induces apoptosis in WR19L12a mouse T lymphoma cell.

The specification provides evidence for HFE7A antibody that specifically binds to SEQ ID NO:1, note 12) above. Although the specification does not give direct evidence, the humanized HFE7A antibodies also have potential to bind to the same epitope. However, throughout the entire 247-page specification, no other molecule except the mouse anti-human Fas HFE7A antibody and humanized HFE7A is disclosed. Based on the antibody alone, one cannot predict the types of other molecules that bind to a conserved, mammalian Fas epitope such as natural Fas ligands or synthetic ligands that bind to the epitope and induces apoptosis. Since the genus includes a large number of unpredictable species, possession of HFE7A and humanized HFE7A is not seen as sufficient to reasonably convey possession of the entire genus. It is concluded that applicants adequately describes HFE7A antibody.

Claim 61 is under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had ***possession*** of the claimed invention. Claim 61 is drawn to a humanized anti-Fas antibody is capable of inducing apoptosis in cells with FasR-ligand system problem, but prevent apoptosis in normal cells. Reference Example 8 (Table 1 at page102) from pages 100 to 103 discloses HFE7A antibody induces apoptosis in normal mouse T cells; it appears that Ch3/HeJ mice used in this experiment is a normal strain and the specification does not describe if this mice strain has FasR-ligand problem. Note page 3042 left column 2nd para of Hartwig et., Blood vol. 99, pages 3041-3049. Also see the specification summary above. The specification does not describe any humanized HFE7A antibody with the functional characteristics specified in claim 61.

Claims 79-81 and 103-105 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had ***possession*** of the claimed invention. Claims 79-81 are drawn to agent comprising various antibodies in claims 62, 67 and/or 68 for preventing or treating rheumatoid arthritis (the elected species). The specification does not teach any molecule that is able to prevent or treat rheumatoid arthritis. Note the specification summary of 14 and 15) above.

Claims 79-81 and 103-105 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to ***enable*** one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 79-81 and 103-105 are drawn to agent comprising various antibodies in claims 62, 67 68, 79, 80, and/or 81 for preventing or treating rheumatoid arthritis (the elected species).

The specification does not teach any agent capable of preventing or treating rheumatoid arthritis. Note the specification summary of 14) and 15) above. Reference Example 9 at pages 103 and 104 discloses MRL gld/gld mice with mutation in gene which serves as "systemic lupus erythematosus-like autoimmue diseases" model, who received HFE7A antibody has less swelling and the antibody also reduces Fas-expressing T cells. Reference Example 12 at page 106 and Fig. 7 disclose that HFE7A reduces symptoms of collagen-induced arthritis in mice and Table 2 at page 109 discloses that HFE7A causes apoptosis of in vitro synovial cells taken from rheumatoid arthritis patients.

One cannot extrapolate the teaching of the specification to the claimed invention because the specification does not teach that method of in vivo Rheumatoid Arthritis treatment. The *in vitro* demonstration of growth inhibition of synovial cells taken from rheumatoid arthritis patients with the antibody produced by HFE7A (Table 2 at page 109) and the in vivo demonstration of either the systemic lupus erythematosus-like autoimmue diseases" (SLE) model or arthritis model cannot be correlated to the invention as claimed, because the specification does not show any in vivo model of rheumatoid arthritis. The antibody *in vitro* assay is in contact with target cells and is not subjected to the defense of the body. In addition, characteristics of cultured cells generally differ significantly from the characteristics of in vivo cells. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, page 4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Thus, based on the in vitro cell data presented in the specification, it could not be predicted that HFE7A could induce treat

rheumatoid arthritis. In addition, agents must accomplish several tasks to be effective in vivo. They must be delivered into the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. Also, the target cell must not have an alternate means of survival despite action at the proper site for the antibody. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The formulation may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life.

Furhte, one cannot extrapolate the teaching of the specification to the claim because it is well known that the art of anti-Rheumatoid Arthritis therapy drug discovery is highly unpredictable. For example, Forre et al (2000, Scand J Rheumatol Vol. 29, pages 73-84) teach that rheumatoid arthritis is notoriously difficult treat. See the entire article, especially the 1st para left column at page 81 for the general state of art for the treatment of rheumatoid arthritis using a similar approach as the invention claimed in the instant application and the first paragraph of the article, which states "Until the cause of rheumatoid arthritis (RA) is further elucidated, a successful prevention or repair of such tissue destruction remains elusive. This statement from the guidelines for the management of RA published by the American College of Rheumatology Ad Hoc Committee on clinical guidelines poses a major challenge to practicing rheumatologists and to the scientific community as a whole."

Considering the lack of sufficient guidance and working examples in the specification, and unpredictability in the art, it is concluded that undue experimentation is necessary to practice the invention.

Claims 1-6, 9, 17, 19, 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while ***being enabling for HFE7A and humanized HFE7A***, does not reasonably provide enablement for any other molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The claims are drawn to a genus of molecules that bind to a conserved Fas epitope (claims

1-6), which is antibody (claims 10 and 11), IgG antibody (claim 16), humanized (claims 17 and 18), and which induces apoptosis in normal and abnormal cells (claim 19). As noted in the specification summary 1)-25) above, the entire specification is dedicated to how to make HFE7A, how to humanize HFE7A as well as binding and apoptotic activities of HFE7A and humanized HFE7A. The specification does not teach any other molecules such as molecules mimicking natural ligands for Fas.

Considering the limited teachings to HFE7A antibody, lack of working examples other than HFE7A antibody, unpredictability in the art, it is concluded that undue experimentation is necessary to practice full scope of the invention.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-6, 8-13, 16, 20, 25, and 41-55, are rejected under 35 U.S.C. **102(b)** as being anticipated by Alderson et al (IDS, 1994, International Immunology, Vol. 6 pages 1799-1806).

The claims are drawn to a molecule that binds to an epitope from Fas antigen conserved between a primate and a non-primate, more specifically between human and mouse (claims 2-5), wherein CDRs of the antibody is identical to the CDR's of HFE7A (claim 8), wherein antibody cross-react with HFE7A (claim 9), wherein claims 10-13 are antibody of claims 1, 6, 8, and 9 respectively, wherein the molecule is IgG in claim 16, wherein the molecule of claim 8 induces apoptosis (claim 19), wherein the molecule of

claim 8 induces apoptosis in normal cells (claim 20), wherein the molecule of claims 1, 6, 8, or 9 binds to SEQID NO:1 epitope (claim 25), wherein the molecule of 1, 6, 8, or 9 is used as an agent for many diseases (claims 41-53), wherein the molecules of claim 1, 6, 8, or 9 induces apoptosis, reduces autoimmune symptoms, does not cause hepatitis, prevents collagen induced arthritis, and/or induce apoptosis in synovial cells from a rheumatoid arthritis (claims 54 and 55). The claims are interpreted as monoclonal mouse anti-human Fas extracellular domain IgG antibody that binds to conserved regions between human and mouse Fas.

The specification at Reference Example 1 at page 68 and also at page 34 describes immunogen preparation by recombinantly producing human Fas extracellular domain fused to other human protein, followed by immunizing mice with the immunogen into mice; this process of making the antibody in the instant claims is identical to the process prepared by Alderson et al (International Immunology, Vol. 6 pages 1799-1806),

Alderson et al, in the first paragraph of the article and in the paragraph bridging pages 1799 and 1800, teach monoclonal mouse anti-human Fas IgG antibody. Alderson et al further teach several clones in Fig. 1-4 and Tables 1 and 2, and teach that the monoclonal mouse anti-human Fas IgG antibodies bind to Fas and induces apoptosis in normal and abnormal cells.

The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that antibodies of the prior art do not possess the same material, structural (for example, claim 8) and functional characteristics (for example, claims 25, 41-55) of the instantly claimed antibody. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed antibody is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claims 1-6, 8-13, 16-20, 22-25, 41-55, and 61 are rejected under 35 U.S.C. **102(a)** as being anticipated by US Pat. 5,620,889 (Apr. 15, 1997).

The claims are drawn to a molecule that binds to an epitope from Fas antigen conserved between a primate and a non-primate, more specifically between human and mouse (claims 2-5), wherein CDRs of the antibody is identical to the CDR's of HFE7A (claim 8), wherein antibody cross-react with HFE7A (claim 9), wherein claims 10-13 are antibody of claims 1, 6, 8, and 9 respectively, wherein the molecule is IgG in claim 16, , wherein molecules of claims 1-15 are humanized (claims 17-18), wherein the molecules of 1-6 wherein the molecule of claim 8 induces apoptosis (claim 19), wherein the molecule of claim 8 induces apoptosis in normal cells (claim 20), wherein humanized molecule drawn specific for Fas antigen conserved between a primate and a non-primate animal is made by routine procedure known in the art (claims 22-24), wherein the molecule of claims 1, 6, 8, or 9 binds to SEQID NO:1 epitope (claim 25), wherein the molecule of 1, 6, 8, or 9 is used as an agent for many diseases (claims 41-53), wherein the molecules of claim 1, 6, 8, or 9 induces apoptosis, reduces autoimmune symptoms, does not cause hepatitis, prevents collagen induced arthritis, and/or induces apoptosis in synovial cells from a rheumatoid arhtrits (claims 54 and 55), wherein a humanized anti-fas antibody is capable of inducing apoptosis, and wherein a humanized anti-Fas is able to induce apoptosis in cells with FasR-ligand system problem, but prevent apoptosis in normal cells (claim 61). The claims are interpreted as monoclonal mouse anti-human Fas extracellular domain IgG antibody and humanized antibody from the mouse anti-human Fas extracellular domain IgG antibody that bind to conserved regions between human and mouse Fas.

US Pat. 5,620,889 teaches monoclonal mouse anti-human Fas IgG antibody (see col. 5, lines 45-68), several clones in Fig. 1-7, Tables 1 and 2, wherein the primate is human (see the abstract), wherein the monoclonal mouse anti-human Fas IgG antibodies bind to Fas and induces apoptosis in abnormal cells expressing Fas and inhibits apoptosis in normal cells (col. 4 lines 44-48), wherein humanized monoclonal anti-human Fas is obtained from CDRs of respective species (col. 5-6), therefore the antibody taught by US Pat. 5,620,889 inherently comprises the CDRs that are able to bind the extracellular domain of human Fas. Also note at Examples 1 and 2 from column 15-17.

The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that antibodies of the prior art do not possess the same material, structural (for example, claim 8) and functional characteristics (for example, claims 25, 41-55) of the instantly claimed antibody. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed antibody is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

In order to obviate this rejection, the certified copies of JP applications (9-82953 and 9-169088, and 9-276064) with their translations should be provided to the Office.

Claims 1-6, 8-13, 16-20, 22-25, 41-55, and 61 are rejected under 35 U.S.C. **102(e)** as being anticipated by US Pat. 5,620,889 (Apr. 15, 1997).

The claims are drawn to a molecule that binds to an epitope from Fas antigen conserved between a primate and a non-primate, more specifically between human and mouse (claims 2-5), wherein CDRs of the antibody is identical to the CDR's of HFE7A (claim 8), wherein antibody cross-react with HFE7A (claim 9), wherein claims 10-13 are antibody of claims 1, 6, 8, and 9 respectively, wherein the molecule is IgG in claim 16, , wherein molecules of claims 1-15 are humanized (claims 17-18), wherein the molecules of 1-6 wherein the molecule of claim 8 induces apoptosis (claim 19), wherein the molecule of claim 8 induces apoptosis in normal cells (claim 20), wherein humanized molecule drawn specific for Fas antigen conserved between a primate and a non-primate animal is made by routine procedure known in the art (claims 22-24), wherein the molecule of claims 1, 6, 8, or 9 binds to SEQID NO:1 epitope (claim 25), wherein the molecule of 1, 6, 8, or 9 is used as an agent for many diseases (claims 41-53), wherein the molecules of claim 1, 6, 8, or 9 induces apoptosis, reduces autoimmune symptoms, does not cause hepatitis, prevents collagen induced arthritis, and/or induces apoptosis in synovial cells from a rheumatoid arhtrits (claims 54 and 55), and wherein a humanized anti-fas antibody is capable of inducing apoptosis, and wherein a humanized anti-Fas is able to induce apoptosis in cells with FasR-ligand system problem, but

prevent apoptosis in normal cells (claim 61). The claims are interpreted as monoclonal mouse anti-human Fas extracellular domain IgG antibody and humanized antibody from the mouse anti-human Fas extracellular domain IgG antibody that bind to conserved regions between human and mouse Fas.

US Pat. 5,620,889 teaches monoclonal mouse anti-human Fas IgG antibody (see col. 5, lines 45-68), several clones in Fig. 1-7, Tables 1 and 2, wherein the primate is human (see the abstract), wherein the monoclonal mouse anti-human Fas IgG antibodies bind to Fas and induces apoptosis in abnormal cells expressing Fas and inhibits apoptosis in normal cells (col. 4 lines 44-48), wherein humanized monoclonal anti-human Fas is obtained from CDRs of respective species (col. 5-6), therefore the antibody taught by US Pat. 5,620,889 inherently comprises the CDRs that are able to bind the extracellular domain of human Fas. Also note at Examples 1 and 2 from column 15-17.

The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that antibodies of the prior art do not possess the same material, structural (for example, claim 8) and functional characteristics (for example, claims 25, 41-55) of the instantly claimed antibody. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed antibody is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

*If applicant could overcome all of rejections above*, claims 1-6, 8-13, 16-20, 22-25, 41-55, and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alderson et al (IDS, 1994, International Immunology, Vol. 6 pages 1799-1806), as applied to claims 1-6, 8-13, 16, 20, 25, and 41-55 above, in view of WO 96/20206 (4 July 1996), and in further view of Green et al (May 1994, Nature Genetics, vol. 7, pages 13-21) and Watanabe-Fukunaga et al (February 15, 1992, The Journal of Immunology, Vol. 148, page 1274-1279).

The claims are drawn to a molecule that binds to an epitope from Fas antigen conserved between a primate and a non-primate, more specifically between human and mouse (claims 2-5), wherein CDRs of the antibody is identical to the CDR's of HFE7A (claim 8), wherein antibody cross-react with HFE7A (claim 9), wherein claims 10-13 are antibody of claims 1, 6, 8, and 9 respectively, wherein the molecule is IgG in claim 16, , wherein molecules of claims 1-15 are humanized (claims 17-18), wherein the molecules of 1-6 wherein the molecule of claim 8 induces apoptosis (claim 19), wherein the molecule of claim 8 induces apoptosis in normal cells (claim 20), wherein humanized molecule drawn specific for Fas antigen conserved between a primate and a non-primate animal is made by routine procedure known in the art (claims 22-24), wherein the molecule of claims 1, 6, 8, or 9 binds to SEQID NO:1 epitope (claim 25), wherein the molecule of 1, 6, 8, or 9 is used as an agent for many diseases (claims 41-53), wherein the molecules of claim 1, 6, 8, or 9 induces apoptosis, reduces autoimmune symptoms, does not cause hepatitis, prevents collagen induced arthritis, and/or induces apoptosis in synovial cells from a rheumatoid arhtrits (claims 54 and 55), wherein a humanized anti-fas antibody is capable of inducing apoptosis, and wherein a humanized anti-Fas is able to induce apoptosis in cells with FasR-ligand system problem, but prevent apoptosis in normal cells (claim 61).

Alderson et al teach mouse monoclonal anti-human Fas IgG antibody (see above 102 art rejection). WO 96/20206 teaches: 1) a soluble form of Fas is detected in patient suffering from systemic lupus erythematosus (SLE) at page 4, 1st para and Example 2 at page 79; 2) antibody specific for Fas at claims 24 and 25 at page 135, how to generate and test monoclonal antibody specific for anti-Fas from page 46-58, Example

VII and VIII; 3) teach usefulness of monoclonal antibody that binds to the soluble form of Fas for diagnosis of human diseases at Example IX at page 92-95, and claims 48-55. Green et al teach at the first line of the article that humanized antibody has lower immunogenicity and more desirable pharmacological properties than engineered mouse antibodies. Watanabe-Fukunaga et al at Figure 5 teach that the part of SEQ ID NO:1 epitope of the instant specification matches to TQNTK (#118-#123) of mouse Fas antigen.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make monoclonal anti-human Fas antibody capable of binding both human and mouse Fas epitopes for minimizing cumbersome generating of monoclonal antibody for mice and human (this way, one can use same antibody for preclinical testing in mice and use it for human later) and humanize it for diagnosing human diseases and for potential pharmaceutical capable of treating notoriously difficult human diseases such as SLE.

## ***Conclusion***

Claims 14, 15, 62-78, 88-90, and 107 are allowable.

Claims 26-29 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Misook Yu whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Misook Yu, Ph.D.
September 9, 2002

MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1800
1600